Adverse Drug Reactions in Modern Cancer Treatment: *What the Non-Oncology Provider Should Know*

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ADR/ADE- ASHP definition

Adverse Drug Event (ADE): harm resulting from medical intervention involving drug- may be preventable or non-preventable; all associated with harm

Adverse Drug Reaction (ADR): a non-preventable ADE occurring with usual use of medication (side effect)

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Grading ADRs

CTCAE (Common Terminology Criteria for Adverse Events)

- Grade 1 = mild to no symptoms, no need for intervention
- Grade 2= moderate symptoms, minimal, local or non-invasive intervention
- Grade 3= severe symptoms but not life-threatening
- Grade 4 = life-threatening
- Grade 5 = death

Traditional chemotherapy:
-not cancer-cell specific
ex: carboplatin, fluorouracil, doxorubicin

Immunotherapy:
- enhance immune response
ex: pembrolizumab, durvalumab, blinatumumab

Targeted Therapy:
-preferentially target tumor cells
ex: trastuzumab deruxtecan, ibrutinib, bevacizumab, olaparib

Traditional Chemotherapy ADRs

Mucositis

Nausea / vomiting / dehydration

Diarrhea

Neutropenic fever

Peripheral neuropathy

Tumor Lysis Syndrome

Immunotherapy: Immune Checkpoint Inhibitors (ICI)

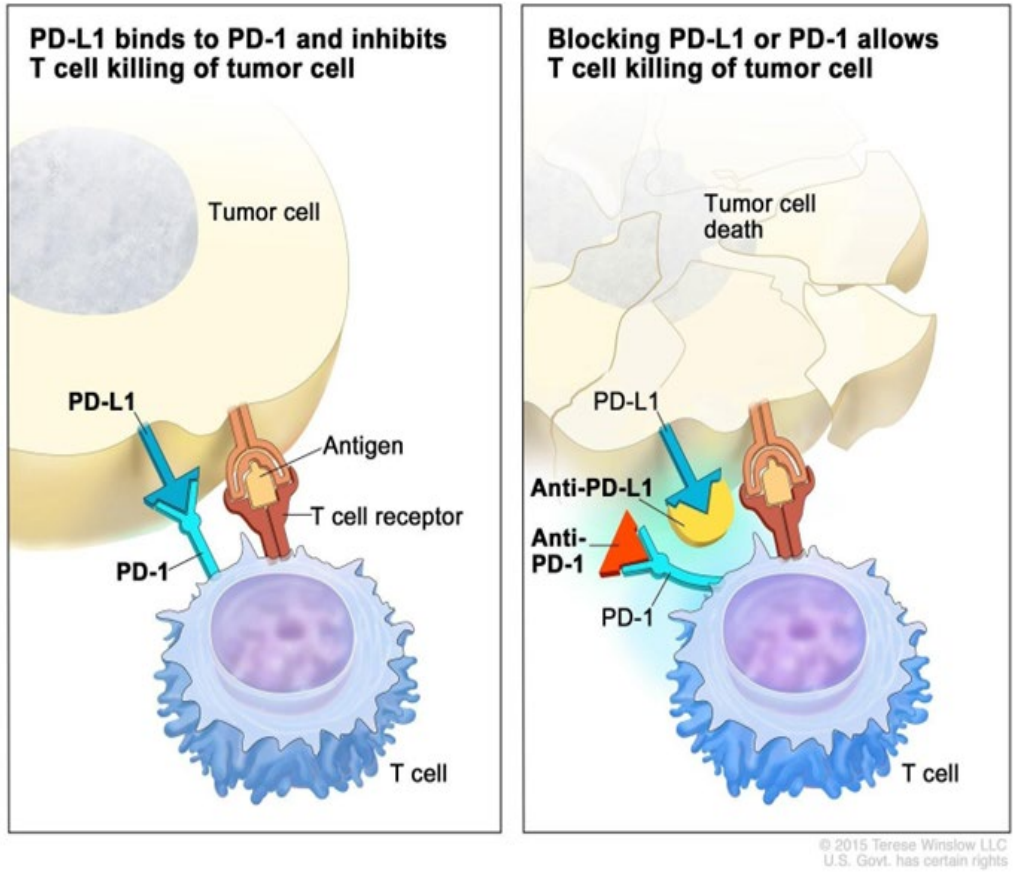
Anti-PD-1 (target programmed cell death-1): Cemiplimab, dostarlimab, nivolumab, pembrolizumab, penpulimab, retifanlimab, tislelizumab, toripalimab

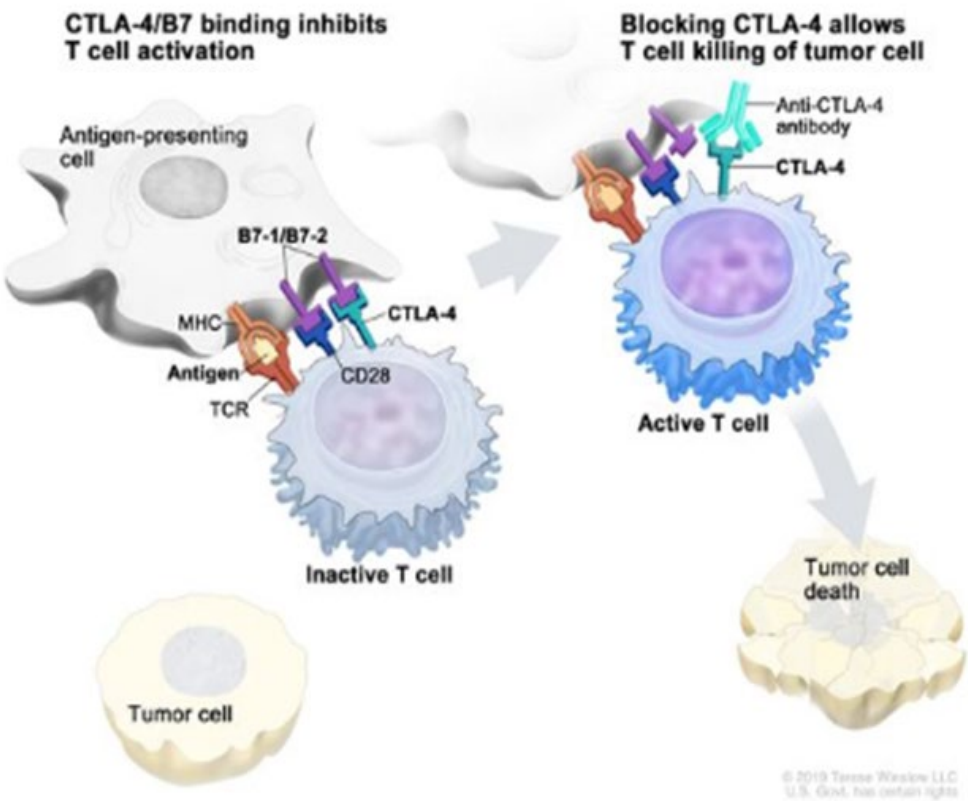
Anti-PD-L1 (target programmed cell death ligand 1): atezolizumab, avelumab, cosibelimab, durvalumab

Anti-CTLA-4 (target cycotoxic T-lymphocyte-associated antigen-4): ipilimaub, tremelimumab

Anti-LAG-3/anti-PD-1: relatlimab and nivolumab

PD-1 and CTLA4 Mechanism of Action





ICI ADRs
-less predictable
-variable from days, to weeks, to after dc
-generally steroid responsive
-early recognition /intervention are key
-multidisciplinary approach recommended
can affect any organ at any time

Incidence of immune-related adverse events (irAEs)

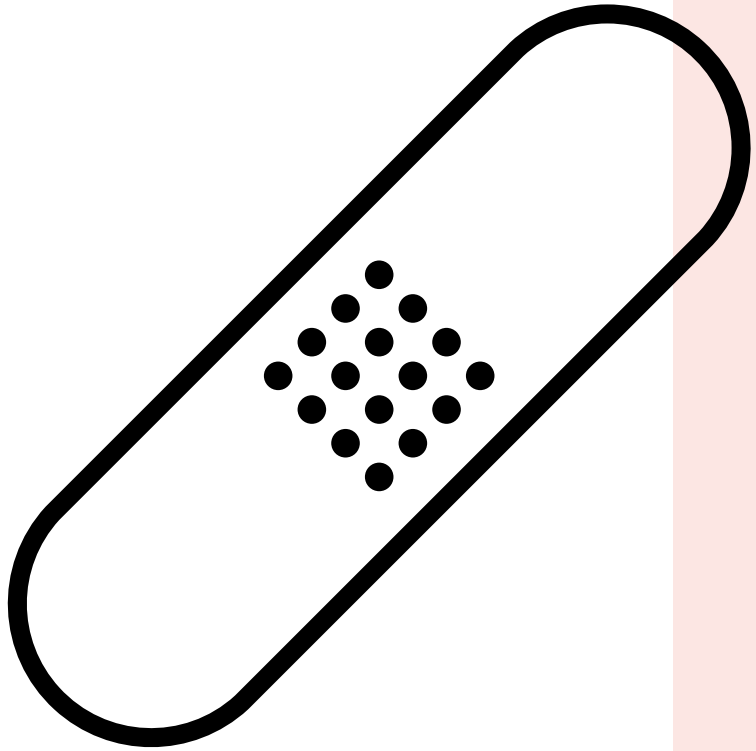
PD-(L)1 as high as 74%

Anti-CTLA-4 as high as 89%

Combination as high as 90%

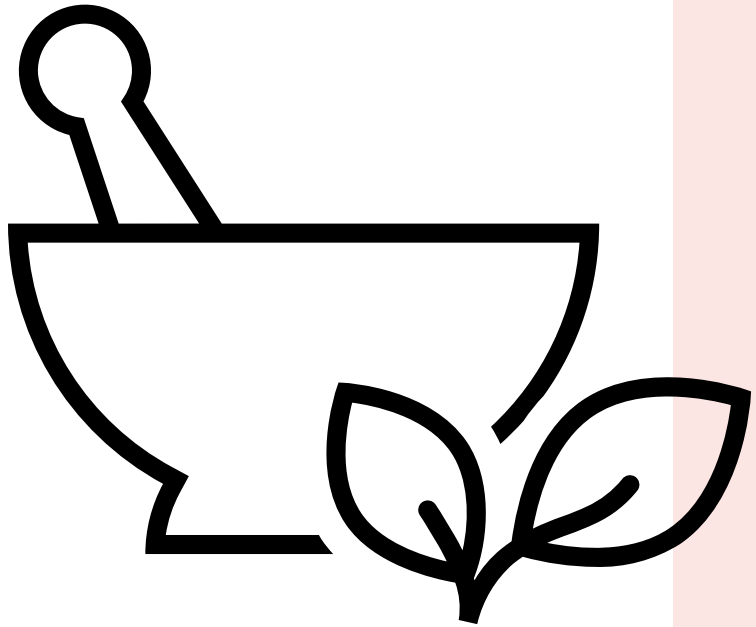
Any Organ, Any Time

- **Skin** up to 70% of patients, more commonly seen with CTLA-4, skin cancer, lung cancer
- Median onset 4 weeks, range 2-150 weeks
- Rash, pruritis, vitiligo, bullous dermatitis, SJS/TEN, lichen planus, psoriasis
- Manage using interprofessional approach with dermatologist; steroids



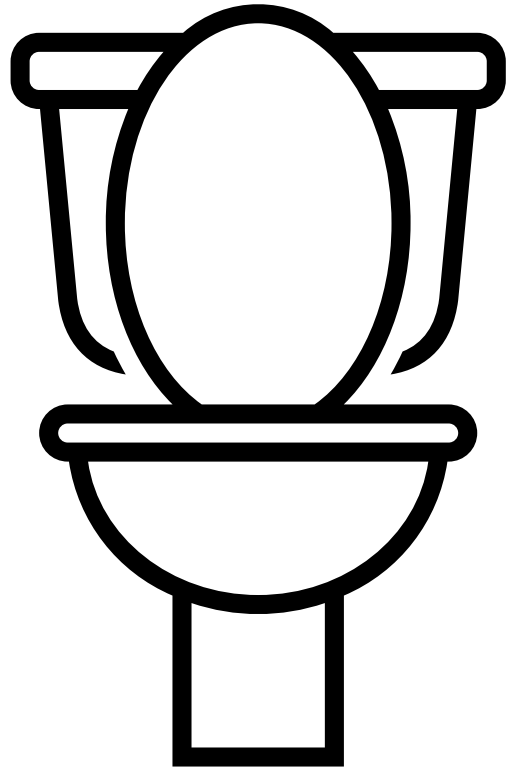
Any Organ, Any Time

- Endocrine – hypothyroidism, hypophysitis, primary adrenal insufficiency, thyrotoxicosis, and type 1 diabetes
- Incidence ~ 10%
- Median onset 14.5 weeks, range 1.5-130 weeks
- Only recommended routine lab monitoring is TSH/FT4
- Symptom monitoring
- Manage with usual treatment and can continue immunotherapy
- Organ dysfunction generally permanent



Any Organ, Any Time

- GI – median onset 6 weeks, range 1-107 weeks
- Diarrhea, colitis, gastritis, enterocolitis, hepatitis, pancreatitis
- Nausea is common, 12% of pd1, 19% of ctla4, 25% combination
- Diarrhea (up to 54%, 8-11% grade >/= 3) and colitis (up to 16%, 11% grade 3 or greater)
- Supportive care for grade 1, grade 2 and higher may require steroids, infliximab, endoscopy/GI consult



Any Organ, Any Time

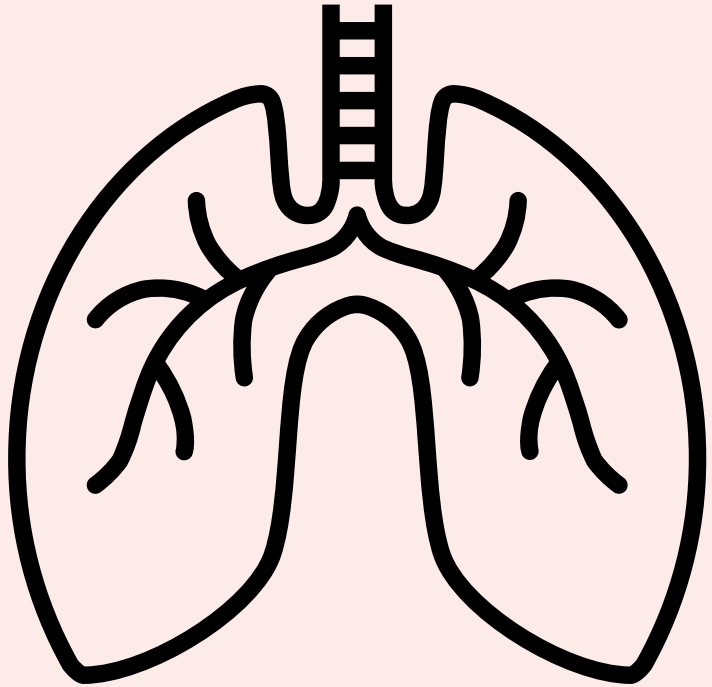
Lungs- ICI pneumonitis

-uncommon but serious

-incidence < 10%, PD1>CTLA4

-can become chronic

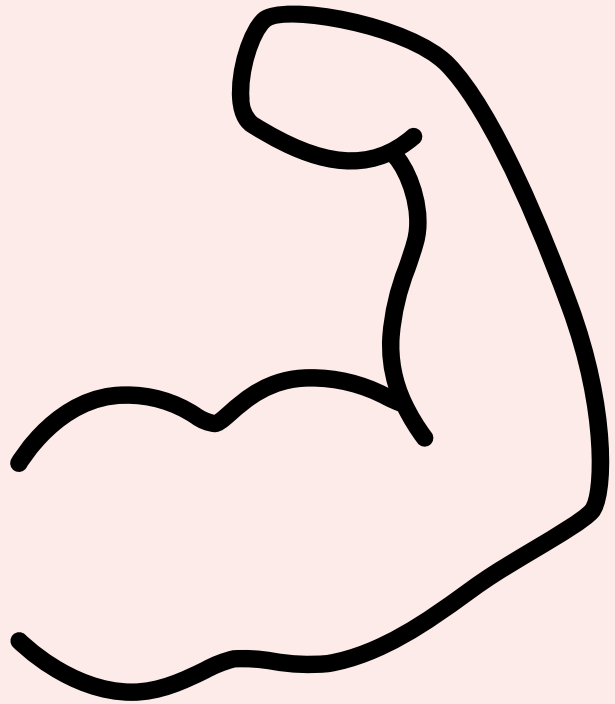
-steroids to manage, if no improvement after 48hrs, its considered refractory



Any Organ, Any Time

Musculoskeletal- inflammatory arthritis, myositis (rare but can be fatal), polymyalgia-like syndrome

- May present as joint pain/swelling, morning stiffness
- Arthralgias and myalgias up to 40%
- Median onset 38 weeks, range 1-127 weeks
- PD1 > CTLA4



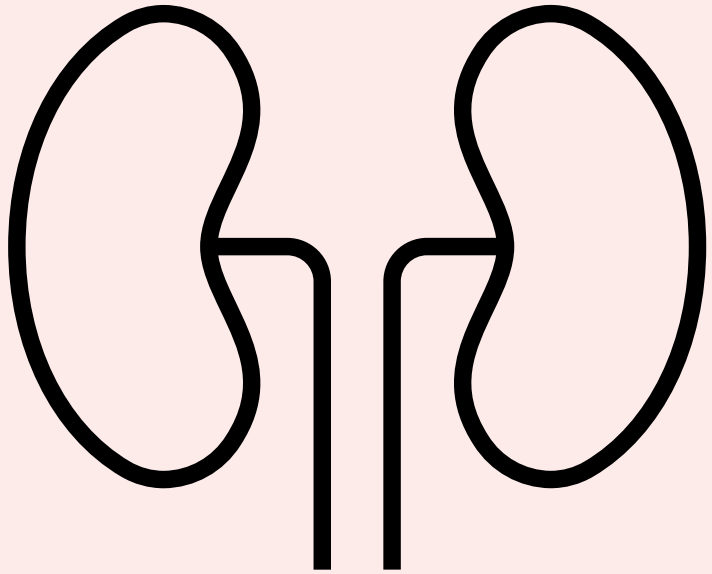
Any Organ, Any Time

Renal

ICI-associated nephritis/AKI is not common, 1-2%

Median time to onset 14 weeks, range 6.5-21 weeks

Treat with steroids



Any Organ, Any Time

CNS

-myasthenia gravis, aseptic meningitis, Guillain-Barre-like syndrome, encephalitis

-median onset 4 weeks, range 1-68 weeks

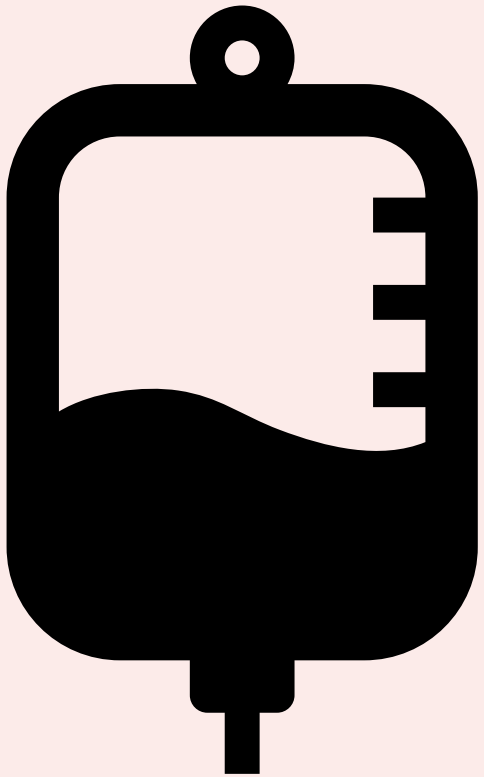
-incidence ~ 1.5%

-peripheral nervous system seems to be affected about twice as often as CNS

Any Organ, Any Time

Hematologic

- thought to not be very common
- May be difficult to distinguish when combined with myelosuppressive chemotherapy
- Median onset 5.7 weeks, range 1-84 weeks
- Hemolytic anemia, TTP, HUS, aplastic anemia, ITP, acquired hemophilia A



Any Organ, Any Time

Cardiovascular

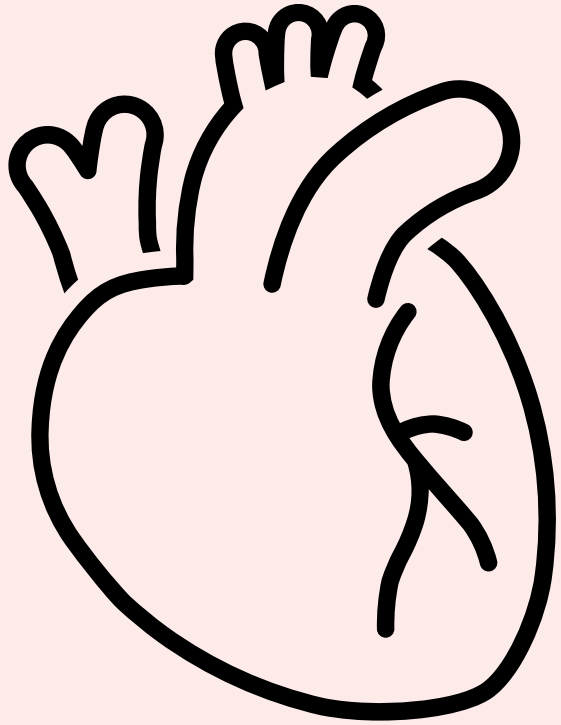
-myocarditis, pericarditis, arrhythmias, heart failure, vasculitis, VTE

-median onset 6 weeks, range 2-54 weeks

-workup should include ECG, troponin, CPK, BNP, echocardiogram, chest x-ray

-rare (<0.1%), but with high mortality

-possibly caused by lymphocytic infiltration of the myocardium and myocardial conduction system



Any Organ, Any Time

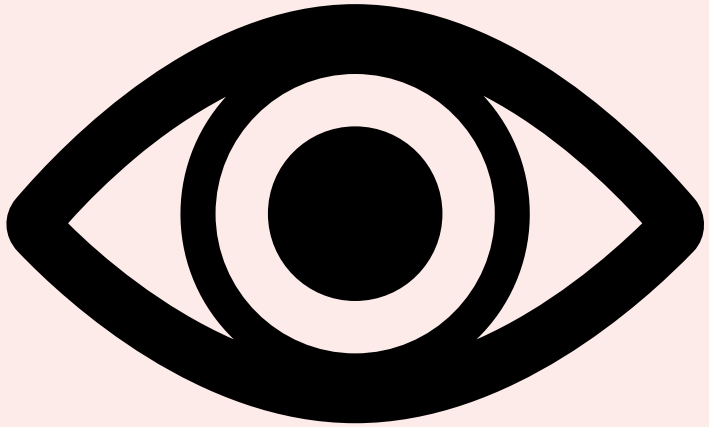
Ocular

-less common

-uveitis, iritis, episcleritis

-median range 5 weeks, range 1-72 weeks

-treat with steroids



General Approach

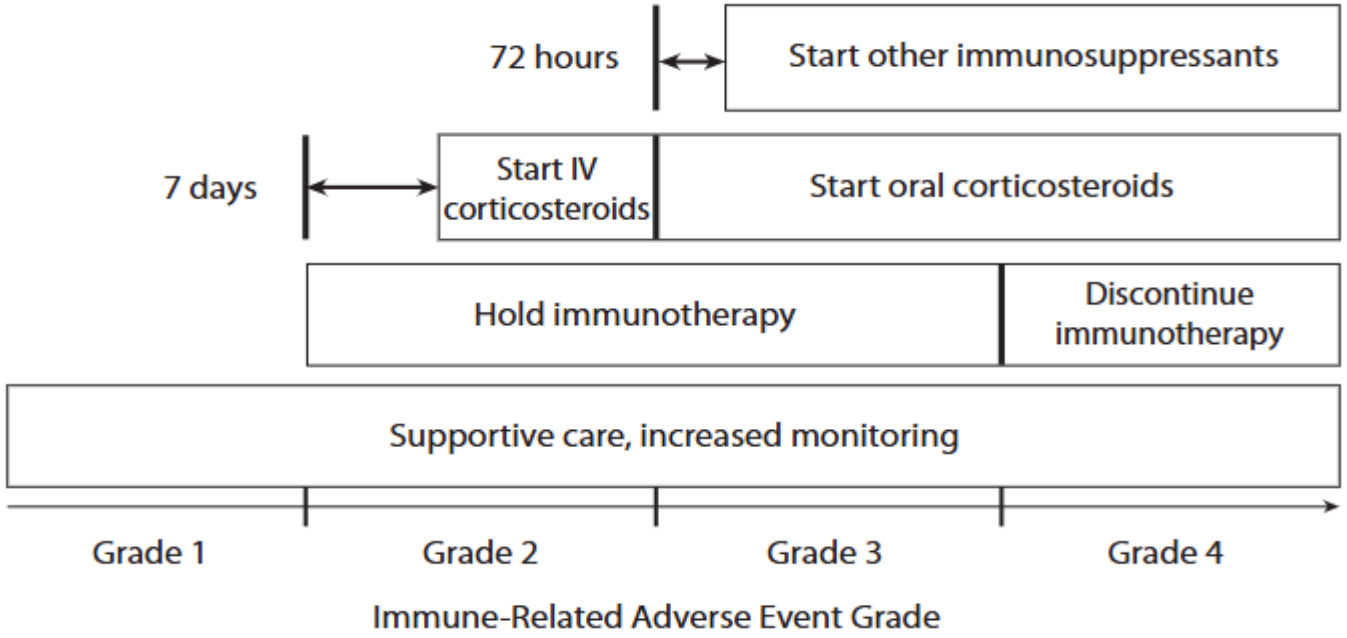
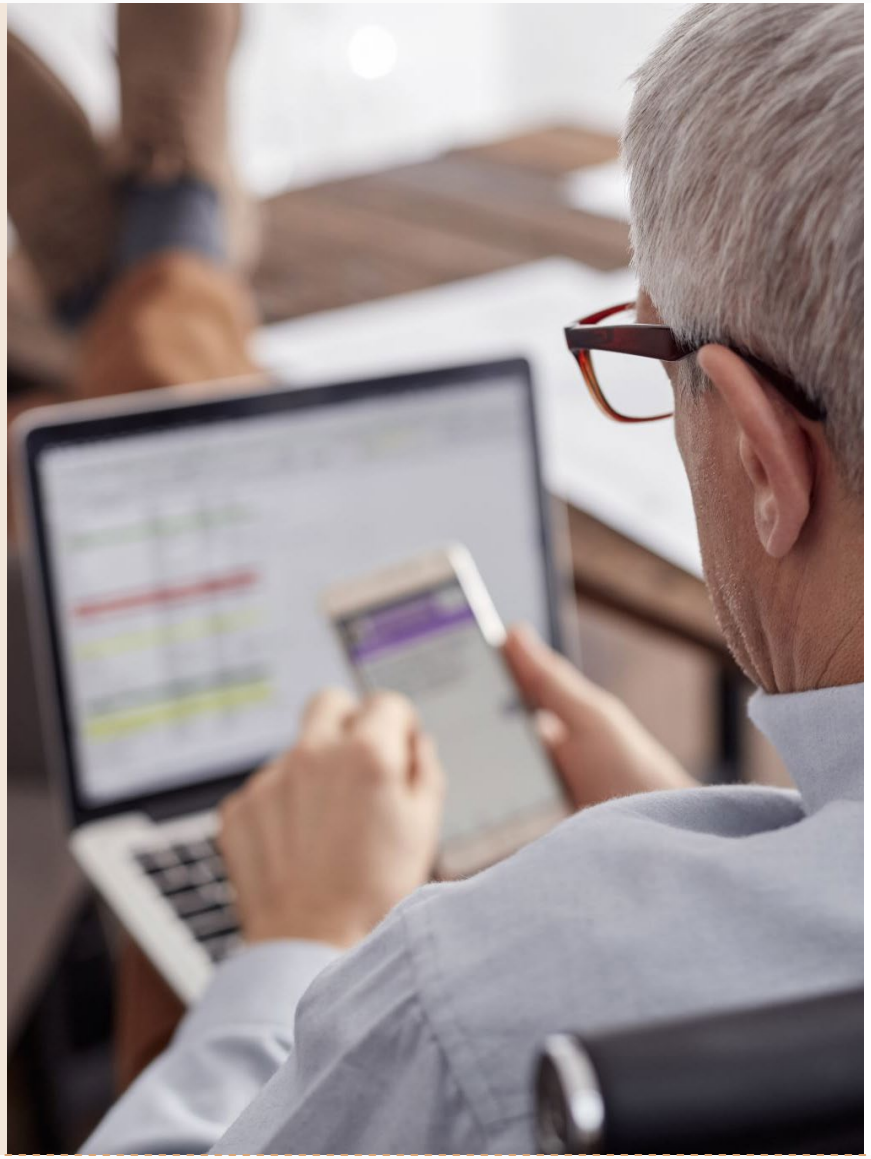


Figure. General approach to the management of immune-related adverse events.
IV, intravenous.

Yun, K. M., & Bazhenova, L. (2023). Management of toxicities associated with immune checkpoint inhibitors. *Clinical Advances in Hematology & Oncology : H&O*, *21*(3), 142–149.



Where to find guidance

Free Access to ASCOs “Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update”

- https://ascopubs.org/doi/full/10.1200/JCO.21.01440

Free NCCN Account:

- www.nccn.org
- NCCN Guidelines->Supportive Care-> Management of Immunotherapy-Related Toxicities

Immunotherapy: Bispecific T-Cell Engagers

- BiTE drugs bind simultaneously to cancer cell antigen and T cells, bringing them together
- Cytokine release syndrome (CRS)
  - Usually occurs during the 1st week, step up dosing to help avoid
  - Can be mild to severe
- Immune cell-associated neurologic syndrome (ICANS)
  - Less frequent
  - Occurs around 7days, often associated with preceding CRS
- Treat with antipyretics, steroids, tocilizumab

Drug Name (Brand)	Targets	Indication
Blinatumomab (Blincyto)	CD3 × CD19	B-cell Acute Lymphoblastic Leukemia (B-ALL)
Teclistamab (Tecvayli)	CD3 × BCMA	Multiple Myeloma
Talquetamab (Talvey)	CD3 × GPRC5D	Multiple Myeloma
Elranatamab (Elrexfio)	CD3 × BCMA	Multiple Myeloma
Epcoritamab (Epkinly)	CD3 × CD20	Large B-cell Lymphoma, Follicular Lymphoma
Glofitamab (Columvi)	CD3 × CD20	Large B-cell Lymphoma
Mosunetuzumab (Lunsumio)	CD3 × CD20	Follicular Lymphoma
Tarlatamab (Imdelltra)	CD3 × DLL3	Small Cell Lung Cancer
Tebentafusp (Kimmtrak)	CD3 × gp100	Uveal Melanoma (HLA-A*02:01+)
Linvoseltamab (Lynozyfic)	CD3 × BCMA	Multiple Myeloma
Solitomab	CD3 × EpCAM	Solid Tumors (colon, gastric, etc.)

Targeted Therapy: Antibody-Drug Conjugates

- Antibody-linker-cytotoxic payload
- Each component can affect the extent of toxicities
  - Pneumonitis/ILD
    - Nonspecific symptoms of SOB, fever, cough
    - Mimics infectious pneumonia
    - Can rapidly progress to life-threatening
    - Treat with steroids
  - Skin toxicities (SJS/TEN)
    - Supportive care, steroids, IVIG
  - Liver failure

Drug Name	Target Antigen	Payload	Indication
Gemtuzumab ozogamicin (Mylotarg)	CD33	Calicheamicin	Acute Myeloid Leukemia (AML)
Brentuximab vedotin (Adcetris)	CD30	MMAE	HL, sALCL, MF, DLBCL
Trastuzumab emtansine (Kadcyla)	HER2	DM1	HER2+ Breast Cancer
Inotuzumab ozogamicin (Besponsa)	CD22	Calicheamicin	B-cell ALL
Moxetumomab pasudotox (Lumoxiti)	CD22	PE38	Hairy Cell Leukemia (discontinued)
Polatuzumab vedotin (Polivy)	CD79	MMAE	DLBCL
Enfortumab vedotin (Padcev)	Nectin-4	MMAE	Urothelial Cancer
Trastuzumab deruxtecan (Enhertu)	HER2	DXd	HER2+ Breast, Gastric, NSCLC
Sacituzumab govitecan (Trodelvy)	Trop-2	SN-38	TNBC, HR+/HER2– Breast Cancer
Belantamab mafodotin (Blenrep)	BCMA	MMAF	Multiple Myeloma (withdrawn)
Loncastuximab tesirine (Zynlonta)	CD19	PBD dimer	DLBCL
Tisotumab vedotin (Tivdak)	Tissue Factor	MMAE	Cervical Cancer
Mirvetuximab soravtansine (Elahere)	FRα	DM4	Ovarian Cancer
Datopotamab deruxtecan (Datroway)	Trop-2	DXd	HR+/HER2– Breast Cancer
Telisotuzumab vedotin (Emrelis)	c-Met	MMAE	NSCLC

Targeted Therapy

There are a wide range of drugs in this category, most are small molecule inhibitors or monoclonal antibodies

- Small molecule inhibitors include many oral chemotherapy drugs:
  - Tyrosine Kinase Inhibitors (TKIs)
  - BRAF Inhibitors
  - PARP Inhibitors (PARPi)
  - VEGF Inhibitors

Monoclonal Antibodies

- CD20 inhibitors
  - Rituximab, obinutuzumab, ofatumumab
- VEGF inhibitors
  - Bevacizumab, ramicurumab
- HER2 inhibitors
  - Trastuzumab, margetuximab, pertuzumab
- EGFR inhibitors
  - Cetuximab, panitumumcab

Targeted Therapy ADRs

- EGFR inhibitors
  - Cetuximab, panitumumab
  - Erlotinib, Osimertinib (oral)
- Dermatologic toxicity (Acneiform rash)
  - 85-95% incidence, median onset 8 days
  - Correlates with response
  - Manage with topical antibiotics and/or steroids
- Diarrhea
  - 20-60% incidence, median onset 12 days
  - Manage with loperamide
- CD-20 Inhibitors
  - Rituximab, Obinutuzumab, Ofatumumab
  - No orals in this category
- Black Boxed Warnings
  - Infusion reactions (~20%, premedicate)
  - Hep B reactivation
  - Progressive multifocal leukoencephalopathy
  - Mucocutaneous reactions

Targeted Therapy ADRs

- VEGF Inhibitors
  - Bevacizumab, ramucirumab
  - Axitinib, cabozantinib, Lenvatinib(oral)
- GI perforation/fistula
- Hemorrhage
- Hypertension
- Proteinuria/nephrotic syndrome
- Thromboembolism
- Impaired wound healing

- HER2 Inhibitors
  - Pertuzumab, trastuzumab, margetuximab
  - Neratinib, tucatinib, lapatinib (oral)
- Common
  - Fatigue
  - Diarrhea
  - Rash
- Black Boxed warning
  - Cardiomyopathy
  - Pulmonary toxicity

Example Case: Myasthenia Gravis

- 78M renal cell carcinoma s/p nephrectomy, started receiving adjuvant pembrolizumab in April
- R eyelid droop started after cycle 2; pt directed to ED where he presented w/unilateral R upper lid ptosis, no other focal/neurologic findings; steroids not started at that time (mild symptoms)
- End of May- neurology consult, w/u for myasthenia, started pyridostigmine. Progressive ptosis + elevated LFTs, tape holding eyelids both sides, severe fatigue;
- 6/11 pt admitted for TAVR, RN notes bil eyelids drooping, tape in place; at this time pt develops severe watery diarrhea w/fecal urgency and incontinence, likely due to pyridostigmine, dose reduced
- One week later pt now experiencing diplopia, no improvement in ptosis, unable to tolerate pyridostigmine, prednisone 0.5 mg/kg daily started
- He then develops myositis w/elevated CK, ESR, CRP and liver enzymes
- He is urgently given IVIG 2 g/kg and symptoms finally begin to resolve, lab results begin to normalize;
- By early August, LFTs WNL, CK normal

Example Case: Dermatologic Toxicity

- 66M, esophageal CA, FOLFOX + trastuzumab + pembrolizumab started in June
- Began to develop rash in January, initially thought to be contact dermatitis due to clothing
- By end of Jan rash is diffuse, erythematous, covering most of torso and extremities; pembrolizumab held, prednisone started
- Rash worsens with prednisone taper; by middle of February, he has evolving skin lesions on abdomen, rash is now on face, no systemic symptoms
- Over the next few months steroids increased, followed by slower taper, rash evolves; trastuzumab held in case it is contributing; eventually on IVIG but pt has severe infusion reaction; pt ends up on cyclosporin which controls/resolves rash, however f/u CT in September indicates progressive disease while off treatment

Example Case: Colitis

- 58F endometrial cancer with mixed response to carbo/paclitaxel, started on lenvatinib + pembrolizumab in July
- Received 2 cycles of pembrolizumab, diarrhea started 1 week after starting lenvatinib
- Diarrhea waxes and wanes, fails loperamide, Lomotil, tincture of opium; steroids help but unable to taper
- Hospitalized multiple times, unable to eat and has significant weight loss, by October she is diagnosed with ICI-induced colitis, somewhat responsive to high-dose IV steroids but fails oral steroids; begins infliximab but never regains enough function to resume treatment and passes away on hospice in December

Example Case: Adrenal Insufficiency

- 53F, breast CA, neoadjuvant pembrolizumab + chemotherapy in 2023
- Had c/o headaches during treatment, some decreased visual acuity
- Hospitalized after C5 for neutropenic fever, had acute hypotension and abdominal symptoms, found to have low AM cortisol and ACTH.
- Continues to follow with endocrinology for ongoing ICI-induced adrenal insufficiency

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Thank You!

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